

## Case Report

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Wang Xiaoqiu, Fang Bingmu\*, Jiang Jinhong, Qu Zhigang, Ma Guangli, Liu Yonghua, Wang Xiaoli

# A case report of hereditary spherocytosis with concomitant chronic myelocytic leukemia

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**Abstract:** Hereditary spherocytosis (HS) and Chronic myelocytic leukemia (CML) are both life threatening hemotologic diseases. They are rarely seen to occur simultaneously in one individual patient. Here we demonstrate a case of HS associated with CML in this study. The patient is a young female, diagnosed with HS in 2005, and was given partial embolization of the splenic artery. She got significant remission after the procedure. In 2008, she was found abnormal in blood routine test, after bone marrow routine, chromosome and fusion gene tests, she was diagnosed with CML (chronic phase). She did not receive regular treatment until 3 months prior, and is currently being treated with Dasatinib. She achieved hematological remission, but had no significant improvement in chromosome and fusion gene figures. Due to her severe condition of hemolysis, a splenectomy or an allogeneic hematopoietic stem cell transplantation is considered.

**Keywords:** Hereditary spherocytosis, Chronic myelocytic leukemia, Case report

## 1 Introduction

HS is the most commonly seen hemolytic disease in hereditary red cell membrane disease. The incidence rate in North Europe and North America can be as high as 1/2000; the overall incidence rate in Caucasians

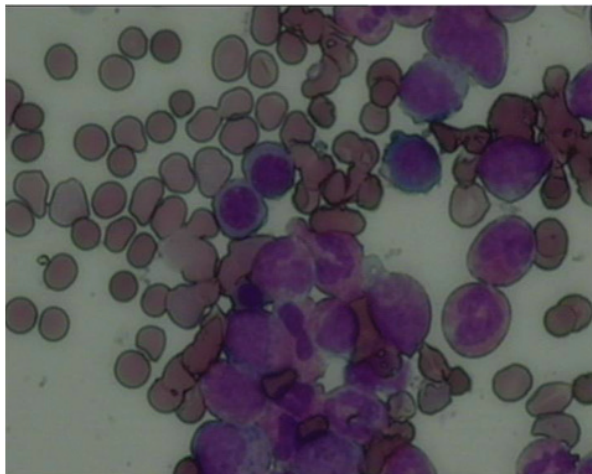
is 1/2000-1/5000[1]. According to the statistics of the Changhai Affiliated Hospital of Shanghai Second Military Medical University, among all the hereditary hemolytic diseases, hemoglobin disease counts for 34%, red cell membrane diseases 43%, and red cell enzyme diseases 23%; HS makes 84% in all the red cell membrane diseases [2]. The featuring chromosome alteration of CML is t (9;22) (q34;q11), hence in molecular level causes the formation of BCR-ABL fusion gene. Concurrent cases of HS and CML is rarely seen in literature reports, here we report our case as follows.

## 2 Case report

The patient is female, 27 years old, with her mother, aunt, and brother and cousin history of HS. She was sent to our hospital in April 2005, for “yellowish discoloration of the sclera and the skin for 3 years, aggravated for 2 months”. Physical examination shows “mild yellowish discoloration of the sclera and the skin, soft abdomen, liver not palpable, spleen is palpable 3cm below the left costal margin. Auxiliary examinations: blood routine test: white blood cell count (WBC)  $8.2 \times 10^9/L$ , red blood cell count (RBC)  $2.84 \times 10^{12}/L$ , hemoglobin (Hb) 92g/L, mean corpuscular hemoglobin concentration (MCHC) 382g/L, platelet count (PLT)  $327 \times 10^9/L$ , proportion of reticulocyte 10.1%; blood smear shows the proportion of spherocytes is 18%; Erythrocyte osmotic fragility test: hemolysis begins at 0.56% salt solution (normal control at 0.42%), complete hemolysis at 0.41% salt solution (normal control at 0.22%); liver function tests: total bilirubin (TB) 163.3umol/L, indirect bilirubin (IB) 154.4umol/L, Lactate dehydrogenase (LDH) 402U/L. computed tomography of the abdomen shows splenomegaly (7 rib units); bone marrow routine test shows significantly active bone marrow proliferation (Figure 1), erythroid proliferation is active, spherocytes are commonly seen, counts for 15%, folic acid, vitamin B12, ferritin, glucose phosphate isomerase, glucose-6-phosphate dehydrogenase test and

\*Corresponding author: Fang Bingmu, Department of Hematology, the People's Hospital of Lishui, Lishui 323000, Zhejiang Province, China, E-mail: chongzhu601@126.com

Wang Xiaoqiu, Jiang Jinhong, Qu Zhigang, Ma Guangli, Liu Yonghua, Wang Xiaoli, Department of Hematology, the People's Hospital of Lishui, Lishui 323000, Zhejiang Province, China

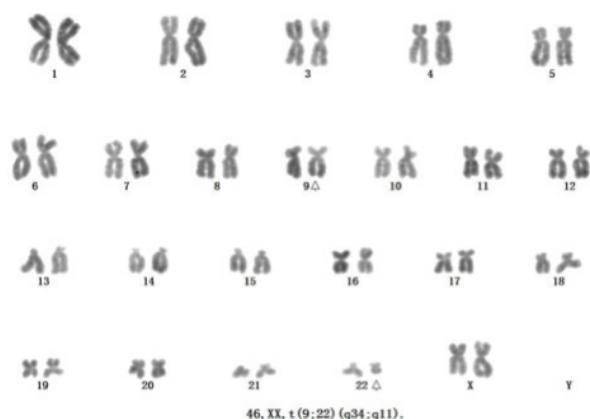


**Figure 1:** Bone marrow smear shows typical chronic

pyruvate kinase tests were normal, Coomb's test shows negative result; normal hemoglobin electrophoresis; expression of CD55 and CD59 on erythrocytes and granulocytes are not significantly below normal range. The clinical diagnosis is: HS. She was given partial embolization of the splenic artery, after which yellowish discoloration of the skin and sclera faded, hemoglobin and bilirubin level returned to normal and splenomegaly relieved.

Yellowish discoloration of the skin and sclera occurred again in September 2007. Auxiliary examination shows: WBC  $12.4 \times 10^9/L$ , RBC  $3.17 \times 10^{12}/L$ , H 108g/L, PLT  $425 \times 10^9/L$ , proportion of reticulocyte 12%; liver function tests: TB 122.3umol/L, IB 108umol/L; upper abdomen CT shows splenomegaly (7 rib units) and splenic embolization postoperative change; bone marrow test gives the same result as the previous one. She received a second partial splenic artery embolization. After the procedure, yellowish discoloration of the skin and sclera faded, hemoglobin and bilirubin level returned to normal and splenomegaly relieved again.

Her blood routine test in February 2008 shows a result of WBC  $69.2 \times 10^9/L$ , the proportion of neutrophils is 74%, RBC  $3.93 \times 10^{12}/L$ , Hb 124g/L, PLT  $575 \times 10^9/L$ , proportion of late promyelocyte is 10%, the proportion of reticulocytes is 11%. Physical examination shows her skin and sclera are mildly yellowish discolored, spleen is enlarged and being palpable 8cm below the left costal margin. Bone marrow test shows extremely active proliferation, Myeloid: erythroid ratio is 8:1, all stages of myeloid cells are increased, especially late promyelocytes, eosinophils and basophils are commonly seen, neutrophil alkaline phosphatase positive rate is 1%, score 2. Chromosome: 46, XX, t(9; 22)(q34; q11) (Figure 2); bone marrow gene test: M-bcr-abl/abl 92%, m-bcr-abl/abl(-). She was diagnosed of CML (chronic phase), and was given



**Figure 2:** Typical chronic myeloid leukemia chromosome changes 46, XX, t(9; 22)(q34; q11)

imatinib therapy for 1 month before recheck her blood routine test: WBC  $7.4 \times 10^9/L$ , RBC  $3.8 \times 10^{12}/L$ , Hb 121g/L, PLT  $344 \times 10^9/L$ . She didn't re-examine chromosome and fusion gene.

**Ethical approval:** The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

**Informed consent:** Informed consent has been obtained from all individuals included in this study.

### 3 Discussion

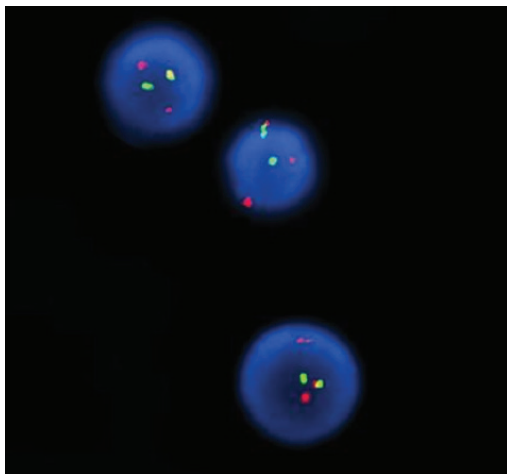
HS is a hereditary hemolytic disease, in most cases is an autosomal dominant trait [3]. The age of onset presents with heterogeneity: it can start from infancy, however in rare cases can start from old age too, which is related to the severity of the defects of the membrane protein. The clinical manifestations of HS are hemolytic anemia of varying degrees, intermittent jaundice, enlargement of the spleen, and significant improvement of symptoms after splenectomy [4]. The hematological characteristics are spherical red blood cell in peripheral blood and significantly elevated red blood cell osmotic fragility [1,5,6].

According to guidelines for the diagnosis and management of hereditary spherocytosis, patient with an HS family history, typical clinical features (e.g. splenomegaly) and peripheral blood index (elevated MCHC and reticulocytes, and presence of spherocytes) can be diagnosed with

HS without further examinations. Approximately 70% of HS are autosomal dominant, 25% are autosomal recessive and 5% are de novo mutations. Even in autosomal dominant cases, most patients need further laboratory tests, for folate deficiency, severe anemia or recent blood transfusions can cover the changes in blood test index. In this case, the patient presents with an HS family history, anemia, jaundice, splenomegaly, elevated MCHC and red blood cell osmotic fragility, elevated reticulocytes, and spherocytes can be seen in peripheral blood. Hence the diagnosis of HS is clear according to 2011 HS guideline.

According to the management recommendations provided in the guidelines, the patient underwent a partial splenic artery embolization, and received good therapeutic effect [7]. Disease relapsed 2 years later, she underwent a second procedure which is still effective, however mild hemolysis has always been present since. During the time she was given 2<sup>nd</sup> generation tyrosine kinase inhibitor (TKI) (nilotinib and dasatinib), her hemolysis exacerbated. This condition has not been reported in literature up to date.

3 years after being diagnosed with HS, she was diagnosed of CML. She has been being treated with imatinib for 1 month, but stopped regular treatment afterwards for various kinds of reasons, she has been pregnant and given birth to a healthy baby girl. After the parturition, her examination results showed she was still in chronic phase. Through 3 months of regular treatment with 2<sup>nd</sup> generation TKI dasatinib, she achieved hematological remission, but gained no improvements in chromosome and BCR-ABL fusion gene (Figure 3). Her treatment response is suboptimal response. The possible reasons for her poor treatment response could be: a. unstandardized and delayed treatment; b. leukemia cells are retained in the enlarged spleen caused by HS; c. drug resistance.



**Figure 3:** Typical chronic myeloid leukemia gene mutation: bcr-abl fusion gene by FISH array

Recently, People's Hospital of Peking University Hematology Institute successfully treated a female case of HS associated with CML by allogeneic hematopoietic stem cell transplantation [8]. After transplantation, the patient's anemia significantly improved, reticulocytes and MCHC went back to normal, BCR-ABL fusion gene is negative, TB level went back to normal. HS has no HLA-identical allogeneic hematopoietic stem cell transplantation contraindications. The patient in our case is currently with serious hemolysis, has been treating with 2<sup>nd</sup> generation TKI for 3 months but hasn't achieved optimal response, HLA-identical allogeneic hematopoietic stem cell transplantation can be a choice, for it cures both of the diseases. Also for this patient, we think splenectomy possibly can also have good effect for her condition.

For this patient, CML occurs during the treatment of HS. Could the occurrence of the two conditions have some sort of association? There are no literature reports exploring the reason, and is still waiting to be studied.

**Conflict of interest statement:** Authors state no conflict of interest.

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